

REMARKS

Claims 99-121 are pending in the application. All claims have been rejected.

Claims 99-102, 104, 108-114 and 116-121 have been rejected under 35 USC 102(b), as anticipated by Arad et al. (US Patent No. 5,534,417). Claims 103, 105 and 106, 107 and 115 have been rejected under 35 USC 103(a), as being unpatentable over Arad et al. (US Patent No. 5,534,417), in view of Kalfon (EP Patent No. 343885), or Hitzman (US Patent No. 4,519,984), or Kobayashi (US Patent No. 5,565,051), or Whitney (GB Patent No. 2,202,549). Claims 99-121 have been rejected for obviousness-type double patenting. Claims 100, 104, 106, 109 have been canceled. Claims 99, 101, 105 and 110 have now been amended. No new subject matter has been introduced.

Double Patenting

The Examiner has rejected claims 99-121 on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1-45 of US Patent No. 6,391,638.

Issues of obviousness-type double-patenting and the submission of a terminal disclaimer will be further considered with respect to US Patent No. 6,391,638 upon indication by the Examiner of allowable claims in the present case.

CLAIM REJECTIONS***35 U.S.C. § 102(b) Rejection over Arad et al (US Patent No. 5,534,417)***

The Examiner has rejected claims 99-102, 104, 108-114 and 116-121 under 35 USC 102(b), as being anticipated by Arad et al (US Patent No. 5,534,417). Claims 100, 104, 106 and 109 have now been canceled, rendering moot the Examiner's rejection thereof. Claims 99, 101, 105 and 110 have now been amended. The Examiner's rejection is respectfully traversed.

The Examiner has alleged Arad et al. disclose a system for culturing cells including a sterilizable, disposable container having a harvester positioned above the bottom of the container, suitable for culturing plant cells and/or plant tissue, which comprises all the essential features of the claimed invention. Applicant disagrees.

Arad et al. discloses a container for growing microalgae outdoors, fashioned of elongated polyethylene cells of generally elliptical shape, which can be aerated

with a gas (air) from a pipe introduced from above, and having a fluid inlet/outlet for filling and emptying. Although Arad et al. state generally that the containers can be used for growing a variety of microorganisms (see "Background", column 1), methods for growing cells other than microalgae are neither suggested nor taught. Examples and all details of all embodiments illustrate the growth of microalgae, to the exclusion of any other life form.

It will be appreciated that the requirements for reactors for culturing microalgae differ significantly from those of reactors designed for culture of isolated plant or animal cells in a completely artificial environment. As noted by Arad et al ("Background"), microalgae commonly grow outdoors in ponds, with limited aeration and minimal movement of the surrounding medium. Indeed, microalgae are photosynthetic, thus removal of oxygen is a concern in the design of the container, as noted by Arad et al.:

"Production in ponds is non-efficient and suffers from problems deriving from poor light penetration, temperature fluctuations...accumulation of oxygen..."(Arad et al. column1)

Surprisingly, however, little detail of gas delivery and exhaust is provided other than describing the bubbling of a gas through pipes from above (see Arad et al., column 4) and a gas outlet for ventilation. Arad et al. is silent regarding bubble size or control of bubble size in the container.

In stark contrast, growing isolated plant cells in culture, in a completely artificial environment, requires finding a careful balance between mixing of the culture, maintenance of adequate concentrations of dissolved oxygen and limitation of the shear forces imposed on the plant cells in culture. In designing the bioreactor as used in the claimed system, despite the availability of techniques for gene manipulation in plant cells, the inventors initially encountered significant difficulty maintaining viable plant cell cultures in a bioreactor, until the parameters of reactor shape, methods of aeration and mixing, and careful control of the size of bubbles were evaluated and optimized.

As detailed in the Declaration of Yoseph Shaaltiel, initial experimentation to determine the parameters allowing efficient growth of plant cells in the bioreactors of

the claimed system required extensive repetition of cultures over greater than two years time. Failure of the early bioreactor designs to support efficient growth of cultured plant cells was evident in the clustering and degeneration of cells in non-continuous, unmixed areas of the reactor, and in the overall poor viability of the cells, which ultimately was found to be a function of the size, number and positioning of the aerating orifices within the reactor, bubble size, and details of the design of the bottom end of the cylindrical reactor. As detailed in the Declaration, optimal culture conditions required the use of a reactor with frusto conical-shaped bottom, elimination of spargers and their replacement with fixed air inlets of at least 4 mm diameter positioned at or near the bottom of the reactor, and provision of a smooth, continuous internal contour, in order to minimize hazardous turbulence and accumulation of cells.

Inasmuch as Arad et al. fails to relate to any of these important parameters in the disclosure, and teaches a method of aeration (pipe provided from above) proven unsuited for use in the reactor of the claimed system, Applicant submits that Arad et al. does not, and cannot anticipate the disposable bioreactor for plant cell culture in the system as claimed. Further, it is Applicant's expert opinion that one of skill in the art, in possession of Arad et al., would not be able to make and use the claimed system for culture of plant cells and production of recombinant plant cell products and metabolites with a reasonable expectation of success.

The abovementioned notwithstanding, and in order to expedite prosecution in this case, Applicant has chosen to amend claim 99 to include the limitations of "wherein said cells and/or tissue are plant cells and/or plant tissue...", as recited in canceled claim 100; and

"...said device comprising at least two air inlets being positioned at or near the bottom end of said device, and wherein said air inlets are designed to produce bubbles comprising a mean diameter of between 1mm and 10 mm..."

as recited in claims 104, 106 and 109.

Inasmuch as Arad et al. fails to teach or suggest a bioreactor for plant cell culture embodying all the limitations of the claimed system, Applicant submits that the 102(a) rejection of the instant claims is improper and respectfully requests

withdrawal of the Examiner's rejection thereof.

35 U.S.C. § 103(a) Rejection over Arad et al (US Patent No. 5,534,417) in view of Kalfon (EP Patent No. 343885), or Hitzman (US Patent No. 4,519,984), or Kobayashi (US Patent No. 5,565,051), or Whitney (GB Patent No. 2,202,549)

The Examiner has rejected claims 103, 105, 106, 107 and 115 under 35 USC 103(a), as being obvious over Arad et al (US Patent No. 5,534,417), in view of Kalfon (EP Patent No. 343885)(103), or Hitzman (US Patent No. 4,519,984)(105,106), or Kobayashi (US Patent No. 5,565,051)(107), or Whitney (GB Patent No. 2,202,549)(115). Claims 100, 104, 106 and 109 have now been canceled, rendering moot the Examiner's rejection thereof. Claims 99, 101, 105 and 110 have now been amended. The Examiner's rejection is respectfully traversed.

The system for culturing plant cells or tissues as claimed includes the following limitations:

- 1) At least one disposable device comprising a sterilisable disposable container which comprises
 - a) a reusable harvester which comprises a flow controller; and
 - b) at least two air inlets being positioned at or near the bottom end of said device, and wherein said air inlets are designed to produce bubbles comprising a mean diameter of between 1 and 4 mm;
- 2) wherein the device can be used continuously for at least one further consecutive culturing/harvesting cycle,
- 3) wherein a remainder of medium containing cells and/or tissue, remaining from a previous harvested cycle, may serve as inoculant for a next culture and harvest cycle,
- 4) wherein said cells and/or tissue are plant cells and/or plant tissue.

Applicant submits that, for the reasons described in detail *supra*, Arad et al. do not teach, suggest or motivate making or using the claimed system for culturing plant cells and/or tissue.

Kalfon (EP 343885) merely teaches manufacturing flexible bioreactors using laminated material.

Hitzman et al (US 4,519,984) merely teaches providing a plurality of bubbling

devices such as spargers, and discloses methods of cooling a fermentation reaction using sparged gasses. Hitzman et al. are silent regarding the design of air/gas inlets, and the resulting size of bubbles. Further, Hitzman et al. are silent regarding bioreactor culture of plant cells and/or tissue.

Kobayashi et al. (US 5,656,015) merely teach the construction of a box-like bioreactor vessel.

Whitney et al. (GB 2 202 549) merely teach the support of bioreactor vessels using a rigid frame.

Applicant submits that inasmuch as Arad et al. fail to teach or suggest the limitations of the plant culture bioreactor of the system as claimed, and that none of the cited publications remedy the shortcomings of Arad et al., Arad et al., alone or in combination with any other references fails to provide evidence for a *prima facie* case of obviousness of the claimed system. Applicant respectfully requests withdrawal of the 103(a) rejections.

In view of the foregoing amendments and remarks, pending claims 99 and claims dependent therefrom are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Respectfully submitted,



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Date: July 8, 2008

Enclosures:

- Petition for Extension (3 Months)
- Declaration and CV of Inventor Shaaltiel